IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:

BARNETT et al.

Serial No.: 09/475,704 Art Unit: 1635

Filing Date: December 30, 1999 Examiner: B. Whiteman

Title: POLYNUCLEOTIDES ENCODING ANTIGENIC HIV TYPE C POLYPEPTIDE, POLYPEPTIDES AND USES THEREOF

DECLARATION PURSUANT TO 37 C.F.R. § 1.132 OF JOHN J. DONNELLY, Ph.D.

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

I, John J. Donnelly, hereby declare as follows:

1. I received my Bachelors of Science Degree in Biology from the University of Pennsylvania in 1975 and a Doctorate of Philosophy Degree in Immunology in 1979 from the University of Pennsylvania. I also have a Masters of Sciences Degree in Strategic Studies from the U.S. Army War College.

2. I am currently Senior Director, Vaccine Research and Development in the Department of immunology & Infectious Diseases at Chiron Corporation and have been at Chiron since 1998. Before joining Chiron, I was Associate Director, Immunology Dept. of Virus & Cell Biology at Merck. Additional details regarding my background and qualifications can be found in the accompanying copy of my *Curriculum Vitae* (Exhibit A).

3. I have reviewed pending Patent Application Serial No. 09/475,704 for "POLYNUCLEOTIDES ENCODING ANTIGENIC HIV TYPE C POLYPEPTIDE, POLYPEPTIDES AND USES THEREOF" by Barnett, et al., (hereinafter "the specification") and the currently pending claims. I have also reviewed the Office Action dated July 18, 2002. Therefore, I am familiar with the issues raised by the Examiner in the Office Action.

4. I understand that the pending claims are directed to expression cassettes comprising nucleotide sequences that encode immunogenic HIV Gag polypeptides. Further, the Gag-encoding nucleotide sequence must exhibit at least 90% identity to the sequences of SEQ ID NOs:1-4. It is further my understanding that the claims are also directed to cells comprising these polynucleotides and to methods of generating an immune response in a subject using the claimed polynucleotide sequences.

5. It is my opinion that, as a technical matter, a skilled worker could have readily made and used the compositions and methods of the pending claims in light of the specification, together with the common general knowledge, tools and methods available in December 1999. I base this opinion on the facts set forth below; however, I call attention to the fact that it was considered routine experimentation at the time of filing to determine a sequence having (i) at least 90% sequence identity to SEQ ID NO:1-4 and (ii) encoding an immunogenic Gag polypeptide; to express such polynucleotides in stem cells or their progenitors; to deliver in a variety of ways such polynucleotides to generate an immune response in a subject. In addition, in drawing my conclusions, I have considered the nature of the claims, the quantity of experimentation required to practice the subject matter of the claims, the existence of working examples, the direction present in the specification, the state of the field at the time the application was filed and the level of skill in the art.

6. At the outset, I note that the term "skilled worker" with a routine level of skill in the filed of molecular biology, immunology and nucleic acid delivery in

December 1999 had a Ph.D. degree and two or more years of post-doctoral training. In view of my training and experience, I am currently, and was in December of 1999, such a skilled worker.

7. In December 1999, the quantity of experimentation required to identify sequences exhibiting 90% identity to SEQ ID NOs:1-4 was quite low. For example, BLAST software programs were commonly known and readily available on the Internet at this time. This set of programs allows for an easy alignment and determination of percent identity as between any sequences. The skilled worker could have easily used the BLAST or any number of other similar programs to determine the percent identity between sequences (in this case between any given sequence and those presented SEQ ID NOs:1-4). The specification also provides extensive guidance in this regard, for example, on page 17, line 3 through page 19. Working examples are also provided, for example comparisons of the claimed sequences to wild-type HIV sequences. (See, Figure 5). Furthermore, the skilled worker could have readily generated any sequence falling within the scope of the claims using routine methods, for example by utilizing PCR to generate sequences, by introducing point mutations and the like. Thus, it is my opinion that it would have required only routine experimentation to determine sequences falling within the 90% identity, as claimed.

8. In addition, the specification provides significant direction for evaluating whether sequences having 90% identity to SEQ ID NO:1-4 encode an immunogenic Gag polypeptide. Those of us working in the field of gene delivery and immunology are well versed in the various tests for determining immunogenicity, which include computer analysis of sequences, comparison to known immunogenic sequences as well as functional tests (*e.g.*, ELISAs, CTL assays and others described in the Examples of the specification). Examples present in the specification demonstrate the generation of sequences and immunogenicity testing of these sequences. (See, Examples 1 and 4).

9. Furthermore, the state of the art in December 1999 was quite sophisticated with regard to determining both sequence identity and evaluating immunogenicity. I have described above some of the tools, programs and methods available in the field of recombinant nucleic acid technology in December 1999 and many other examples of homologous nucleic acid molecules that encode immunogenic proteins were also available. Therefore, it is my opinion that, following the guidance of the specification, a scientist could have readily made and used polynucleotide sequences that exhibit at least 90% sequence identity to SEQ ID NO:1-4 and which encode an immunogenic HIV Gag polypeptide.

10. Preparing polynucleotides encoding immunogenic Gag polypeptides in December 1999 was a predictable art. There is no doubt that a skilled worker would have been able to make and use sequences exhibiting 90% identity to SEQ ID NO:1-4 and encoding an immunogenic polypeptide. Even if a rare construct were inoperable for some reason (*e.g.*, it wasn't immunogenic), the skilled worker would have readily modified the construct according to the alternatives available at the time and described in the specification. In other words, to the skilled worker, an inoperable construct would itself be a useful starting material for other operable constructs. Essentially all molecules that fall within the claims would be useful for making or using defining technical features of the claims, *i.e.*, nucleotide sequences having 90% sequence identity to SEQ ID NO:1-4 and which encoded an immunogenic HIV Gag polypeptide.

11. Similarly, the specification as filed clearly provides ample guidance on how to generate an immune response (humoral and/or cellular) in a subject by administering the claimed sequences. (See, page 7, lines 9 to 20; page 12, line 28 to page 13, line 15; and Examples 4 and 7). Indeed, in December 1999, it was predictable and routine to evaluate whether an immune response was generated against a polypeptide antigen encoded by an administered polynucleotide, for example using the techniques and tools described above in paragraph 8. Furthermore, the skilled worker would know that

generating an immune response does not necessarily mean that the subject will be vaccinated – *i.e.*, protected against HIV infection or derive some therapeutic benefit. The skilled worker would also have known that immune responses are useful for numerous scientific purposes, such as laboratory assays, preparing reagents for virologic and immunologic studies, analyzing immune responses, and preparation of diagnostic kits. Therefore, a skilled worker would have known that the claimed sequences could be used for additional scientific purposes other than seeking protective immunity or a therapeutic benefit. In view of the guidance in the specification, the predictability and state of the art, and high level of the skilled worker, it is plain that it would have been routine to administer a polynucleotide and evaluate whether or not an immune response to the encoded polypeptide was generated in the subject.

12. Moreover, in the course of further work on HIV, the inventors have evaluated the immune responses generated upon administration of the claimed Gag-encoding polynucleotide constructs to subjects. The manuscript attached hereto (Exhibit B) shows that the claimed expression cassettes generate both humoral and cellular responses when made and administered to animal subjects as described in the specification. (See, for example, Figures of Exhibit B and text describing these Figures). Specifically, this manuscript demonstrates that neutralizing antibodies develop more rapidly in animals vaccinated with the claimed constructs; that these neutralizing antibodies correlated with lower peak viremia after pathogenic virus challenge; and that the claimed Gag-encoding constructs generate cellular immune responses. Thus, although not required by the claims, the claimed constructs are, in fact, able to generate potentially "protective" immune responses. Accordingly, a skilled worker could readily practice the claimed methods of generating an immune response in view of the teachings of the specification and state of the art as filed.

13. It would have also been routine to express the claimed Gag-encoding polynucleotides in stem cells or lymphoid progenitor cells. The guidance in the

specification in this regard is extensive. (See, Section 2.3.2 starting on page 61 of the specification). In addition, the level of skill in this field was very high at the time of filing, the state of the art sophisticated and the experimentation needed to get expression in lymphokine cells (such as stem cells and lymphoid progenitor cells) was routine using standard vectors (*e.g.*, plasmids such pBR322 and pBLUESCRIPT that include promoters and other control elements). Even a reference cited in the Office Action makes it clear that heterologous HIV polypeptide-encoding sequences can readily be introduced into and expressed in stem cells:

> Other areas where gene transfer into hematopoietic cells is being investigated include human immunodeficiency virus (HIV) infection ... the importance of these studies cannot be over emphasized as they provide 'proof-in-principle' that gene-marked cells can survive and be expressed for extended periods of time once re-introduced into the host. (Prince, *Pathology* 30:335-347 at page 340, left column, emphasis added).

Therefore, the specification teaches a skilled worker how to express the claimed Gag-encoding sequences in stem cells or progenitors of lymphoid cells.

14. Finally, I believe that, following the teachings of the specification and guidance of the art, a skilled worker could have readily administered the claimed nucleic acids specification by a variety of modes including intramuscular, intradermal, mucosal and the like. The quantity of experimentation required to use alternatives to intramuscular delivery routes was quite low in December 1999. A skilled worker could have easily administered polynucleotides by a variety of routine methods known at the time of filing. For example, administration of polynucleotides encoding HIV antigens via intradermal and mucosal modes is described in Shiver et al. 1997 *Vaccine* 15:884-887 (Exhibit C) and Durrani et al. 1998 *J. Immunol. Methods* 220:93-103 (Exhibit D). These references are clearly representative of the high level of skill in the art and the fact that non-intramuscular modes of administration were considered predictable in December 1999 -- many of the examples gene delivery modes were also known. Furthermore, at the

time of filing, it was known in the art that administration of polynucleotide vaccines by diverse routes such as intradermal, transdermal, intranasal, oral and the like did not require special modifications to the coding sequence of the polynucleotide plasmid construct itself. The specification provides significant direction in these regards as well, for example on page 61 of the specification. Therefore, a skilled worker would have found the claimed expression cassette and sequences at least 90% identical to it to be useful for generating an immune response using diverse routes and methods. Thus, to the skilled worker, administering the claimed polynucleotides by any number of delivery routes would have been routine and required only minor experimentation.

15. In view of the foregoing facts regarding the routine nature of experimentation required to make and use the claimed constructs, the extensive direction provided by the specification, the straightforward nature of the invention, the presence of working examples, the high level of the skilled worker, the sophistication of the art, and the predictability (*e.g.*, of determining sequences identity and immunogenicity) of the art, it is my unequivocal opinion that the specification enabled, in December 1999, a skilled worker to make and use the subject matter of the claims.

16. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

11/20/02
Date

John J. Donnelly, Ph.D.